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EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/728,509	ZHANG ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9 and 11-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,11-14,17 and 18* is/are rejected.

7)☒ Claim(s) *15,16 and 19* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4-3-08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *SEQ Alignment Data*.

DETAILED ACTION

This Office action is in response to the communication filed 4-3-08.

Claims 1-9, 11-19 are pending in the instant application.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4-3-09 has been entered.

Response to Arguments and Amendments

Applicant's arguments with respect to the pending claims have been considered but are moot in view of the new ground(s) of rejection set forth below.

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

Rejections Necessitated by Amendments

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1, 2, 11 and 13 are rejected under 35 U.S.C. 102(e) as being anticipated by Baxter et al (WO 03/006029).

Baxter et al (WO 03/006029) teach a composition comprising a pharmaceutically acceptable diluent and an antisense oligonucleotide between 12-30 nucleobases comprising at least 8 consecutive nucleobases of SEQ ID NO. 64, and which oligonucleotide is 100% complementary to SEQ ID NO. 17 (see Accession No. ABX13068 and page 19 of Baxter et al; see accompanying alignment data between Acc. No. ABX13068 and SEQ ID NO. 64).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-9, 11-14, 17 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baxter et al (WO 03/006029) as applied to claims 1, 2, 11 and 13 above, in view of Korsmeyer (USPN 6,500,626) and further in view of Milner et al and McKay insofar as the claims are drawn to compositions and methods of inhibiting the expression of the BCL2-associated x protein in vitro comprising administration of a composition comprising a pharmaceutically acceptable diluent and an antisense oligonucleotide between 12-30 nucleobases in length comprising at least 8 consecutive nucleobases of SEQ ID NO: 64 and which oligonucleotide is 100% complementary to SEQ ID NO. 17, which oligonucleotide comprises a phosphorothioate internucleotide linkage, a 2'-O-methoxyethyl sugar moiety and a 5'methyl-cytosine, and which is optionally a chimeric oligonucleotide, and which composition further comprises a colloidal dispersion system and gap segment consisting of ten linked deoxynucleotides, a 5' wing segment consisting of five linked nucleotides, a 3' wing segment consisting of five linked nucleotides, and which gap segment is between the 5' and 3' wings, and each wing comprises a 2'-O-methoxyethyl sugar and wherein each internucleoside linkage is a phosphorothioate linkage.

Baxter et al (WO 03/006029) is relied upon as cited in the 102 rejection above.

Baxter does not teach antisense oligonucleotides comprising phosphorothioate internucleotide linkages, 2'-O-methoxyethyl modified sugar moieties or 5-methyl cytosine nucleobases, nor chimeric antisense oligonucleotides, nor colloidal dispersion systems, gapmers.

Korsmeyer (6,500,626) teach the inhibition of expression of SEQ ID No. 17, encoding the BCL2-associated x protein, using antisense oligonucleotides (see col. 29 and col. 46, lines 54-56).

Milner et al (Nature Biotech. 15: 537-541, 1997) teach methods of designing and testing antisense oligonucleotides for their ability to specifically hybridize and inhibit the expression of a target nucleic acid of known nucleotide sequence in vitro, including in the 5', 3' and stop codon regions of the target gene (See figure 1 on p 538 and figures 5-7 on pages 539-540).

McKay et al (USPN 6,133,246, 10-17-00) teach colloidal dispersion compositions comprising antisense oligonucleotides between 12 and 30 nucleobases in length which optionally comprise modified internucleotide linkages including phosphorothioate linkages, modified nucleobases including 5-methylcytosine, modified sugar moieties including 2'-O-methoxyethyl sugars, and wherein the antisense is optionally a chimeric oligonucleotide, and antisense oligonucleotides optionally design choices of modifications comprising 5' wing segments consisting of five linked nucleotides, 3' wing segments consisting of five linked nucleotides, and a gap segment between the 5' and 3' wings, wherein

each wing comprises a 2'-O-methoxyethyl sugar and wherein each internucleoside linkage is a phosphorothioate linkage, and which antisense targets various regions of a target gene. McKay et al also teach the in vitro inhibition and screening of modulators (*e.g.* of various antisense oligonucleotides between 12-30 nucleobases that specifically hybridize with the target gene).

It would have been obvious to one of ordinary skill in the art to design and utilize antisense oligonucleotides between 12-30 nucleobases in length comprising at least 12 contiguous nucleobases of SEQ ID NO. 64 to inhibit the expression of SEQ ID No. 17, encoding the BCL2-associated x protein (BAX) in vitro, because Baxter teaches this antisense sequence, and Milner et al and McKay teach the ability to design and assess antisense oligonucleotides for their ability to inhibit the expression of a target gene of known nucleotide sequence in vitro, including various regions of the target gene of interest, using routine screening assays that are well known in the art (see Milner at pages 539-540 and McKay at col. 6-15). It would have been obvious to one of ordinary skill in the art to target and inhibit the expression of BCL2-associated x protein in vitro comprising the administration of antisense oligonucleotides between 12-30 nucleobases because Baxter teaches such an antisense oligonucleotide, and antisense of this size range, directed to a target gene of known sequence were well known in the art for targeting and inhibiting the expression of a known target gene, and Milner teaches methods of designing and assessing antisense oligonucleotides between 8-50 nucleobases for their ability to target and inhibit the expression of a known target gene in vitro. One of ordinary skill in the art

would have been motivated to utilize such a method of finding optimal antisense oligonucleotides between 12-30 nucleobases which best target and inhibit BCL2-associated x protein expression in order to study this target molecule's role in apoptosis, and its role in pathologies related to aberrant expression of BAX, including such conditions as Parkinson's, Alzheimer's.

One of ordinary skill in the art would have expected that the methods of designing and assessing antisense oligonucleotides for inhibiting a target gene of known sequence, which were taught by Milner et al, and also taught by McKay to be routine for a previously characterized target gene, would successfully be used to identify numerous antisense oligonucleotides (between 12-30 nucleobases) for the in vitro inhibition of BCL2-associated x protein expression. One of ordinary skill in the art would have been motivated to incorporate the nucleobase, internucleotide linkage and sugar modifications, as well as chimeric structures, into antisense oligonucleotides because such modifications (including 5-methyl cytosine, 2'-O-methoxyethyl and phosphorothioate linkages) have been taught previously by McKay et al to increase target binding, cellular uptake and antisense stability. One of ordinary skill in the art would have expected that the delivery of modified antisense oligonucleotides to target cells harboring BCL2-associated x protein, which antisense specifically hybridize with the target nucleic acid encoding BCL2-associated x protein (e.g. of the 3' UTR of SEQ ID No. 17), would lead to inhibition of expression of BCL2-associated x protein in vitro.

Therefore, the invention as a whole would have obvious to one of ordinary skill in the art at the time the invention was made.

Allowable Subject Matter

Claims 15, 16 and 19 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. ' 1.6(d)). The official fax telephone number for the Group is 571-273-8300. NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jane Zara whose telephone number is (571) 272-0765. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz, can be reached on (571) 272-0763. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information

for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jane Zara
5-15-08
/Jane Zara/
Primary Examiner, Art Unit 1635